

PMP22 Gene

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peripheral myelin protein 22

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1. Introduction

The *PMP22* gene provides instructions for making a protein called peripheral myelin protein 22 (PMP22). This protein is found in the peripheral nervous system, which connects the brain and spinal cord to muscles and to sensory cells that detect sensations such as touch, pain, heat, and sound.

The PMP22 protein is a component of myelin, a protective substance that covers nerves and promotes the efficient transmission of nerve impulses. The protein is produced primarily by specialized cells called Schwann cells that wrap around and insulate nerves. Within Schwann cells, PMP22 plays a crucial role in the development and maintenance of myelin. Studies suggest that the PMP22 protein is particularly important in protecting nerves from physical pressure, helping them restore their structure after being pinched or squeezed (compressed). Compression can interrupt nerve signaling, leading to the sensation commonly referred to as a limb "falling asleep." The ability of nerves to recover from normal, day-to-day compression, for example when sitting for long periods, keeps the limbs from constantly losing sensation. The *PMP22* gene also plays a role in the growth of Schwann cells and the process by which cells mature to carry out specific functions (differentiation).

Before they become part of myelin, newly produced PMP22 proteins are processed and packaged in specialized cell structures called the endoplasmic reticulum and the Golgi apparatus. Completion of these processing and packaging steps is critical for proper myelin function.

2. Health Conditions Related to Genetic Changes

2.1. Charcot-Marie-Tooth disease

Mutations in the *PMP22* gene cause several forms of a neurological disorder called Charcot-Marie-Tooth disease. This disorder damages the peripheral nerves, which can result in loss of sensation and wasting (atrophy) of muscles in the feet, legs, and hands.

An extra copy of the *PMP22* gene in each cell caused by a duplication of genetic material on chromosome 17 is the most common genetic change that causes Charcot-Marie-Tooth disease type 1A (CMT1A). The extra gene leads to an overproduction of PMP22 protein. The connection between excess PMP22 protein and the signs and symptoms of CMT1A is unclear. Research suggests that excess PMP22 protein may overwhelm the cells' ability to process it correctly, leading to a buildup of unprocessed, nonfunctional protein. This buildup may impair the formation of myelin and disrupt other Schwann cell activities, leading to instability and loss of myelin (demyelination). Demyelination reduces the ability of the peripheral nerves to activate muscles used for movement or relay information from sensory cells back to the brain. Typically beginning in adolescence, affected individuals experience atrophy of the muscles of the lower legs and hands and decreased sensitivity to touch, heat, and cold.

CMT1A is also caused by mutations that add, delete, or change the building blocks (amino acids) used to make PMP22 protein. The altered protein is probably processed at a slower rate, and some of the protein is processed abnormally. These disruptions of PMP22 processing impair the normal functions of the Schwann cell, leading to demyelination and producing the signs and symptoms of CMT1A.

In addition to muscle and sensory problems, hearing loss is experienced by some people with a form of Charcot-Marie-Tooth disease called type 1E (CMT1E). CMT1E is associated with particular amino acid substitutions and deletions in the *PMP22* gene. The most frequently reported mutation causing hearing loss replaces the amino acid alanine with the amino acid proline at protein position 67 (also written as Ala67Pro).

Some mutations in the *PMP22* gene cause a severe form of Charcot-Marie-Tooth disease sometimes referred to as Dejerine-Sottas disease or type 3 Charcot-Marie-Tooth disease. This form of the disorder usually begins in infancy, causing muscle weakness and atrophy and delayed development of motor skills such as walking. The mutations that cause this form of Charcot-Marie-Tooth disease are thought to reduce the amount of functional PMP22 protein in cells. It is unclear why they cause more severe features than the mutations that cause CMT1A. Studies suggest that cell function is sensitive to the amount of PMP22 protein, and that having either too much or too little of this protein can cause disease.

2.2. Hereditary neuropathy with liability to pressure palsies

Loss (deletion) of one copy of the *PMP22* gene from each cell is the most common genetic cause of hereditary neuropathy with liability to pressure palsies. This disorder is characterized by recurrent episodes of numbness, tingling, or loss of muscle function, usually triggered by pressure on a nerve in an arm or leg. Deletion of one copy of the *PMP22* gene reduces the amount of PMP22 protein produced by about half. This disorder can also be caused by *PMP22* gene mutations that change single amino acids in the PMP22 protein or that lead to production of an abnormally small protein that is rapidly broken down. The consequences of a shortage of PMP22 protein are not clearly understood. Shortage of PMP22 protein may affect the structure of the myelin covering, impairing the transmission of nerve impulses. In addition, nerves are less able to recover from compression, which also interrupts nerve signaling, causing the signs and symptoms of hereditary neuropathy with liability to pressure palsies.

2.3. Yuan-Harel-Lupski syndrome

Having an extra copy of the *PMP22* gene in each cell is thought to underlie many of the major features of Yuan-Harel-Lupski (YUHAL) syndrome, which is characterized by multiple neurological problems. Some features of this condition, particularly muscle weakness and decreased sensitivity to touch, heat, and cold in the lower legs and feet, are similar to those of CMT1A (described above). Other features of YUHAL syndrome include delayed development and behavioral problems.

YUHAL syndrome results from abnormal copying (duplication) of a small piece of the short (p) arm of chromosome 17 in a region designated p12-p11.2. In YUHAL syndrome, the duplicated segments can range in size from 3.2 million DNA building blocks (also written as 3.2 megabases or 3.2Mb) to 19.7Mb. These segments contain the *PMP22* gene, a nearby gene called *RAI1*, and sometimes additional genes.

As in Charcot-Marie-Tooth disease, an extra copy of the *PMP22* gene leads to nerve problems that cause lower leg and foot abnormalities. Duplication of the *RAI1* gene accounts for delayed development, behavioral problems, and some of the other abnormalities characteristic of YUHAL syndrome.

3. Other Names for This Gene

- GAS-3
- GAS3
- growth arrest-specific 3
- HNPP
- MGC20769
- PMP22_HUMAN
- Sp110

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